Prostatic Intraepithelial Neoplasia in a 53-Year-Old Man

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CASE REPORT

A 53-year-old man with a prostate-specific antigen (PSA) level of 4.2 ng/dL has a benign 40 g prostate on digital rectal examination. The patient undergoes a 12-core biopsy of the prostate, which shows a single focus of prostatic intraepithelial neoplasia (Figure 1).

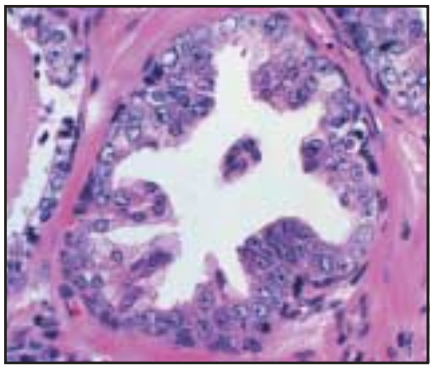

Figure 1. *High-grade prostatic intraepithelial neoplasia: micropapillary pattern (hematoxylin and eosin, × 400).*

MANAGEMENT OPTIONS

The next appropriate step in the management of this patient would be:

❑ 1. Immediate repeat 12-core biopsy

❑ 2. Immediate repeat saturation biopsy

❑ 3. Immediate repeat biopsy of transition zone

❑ 4. Repeat biopsy in 1 year

❑ 5. Repeat biopsy in 3 years independent of PSA change

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Discussion of Last Issue's Case Scenario

In the Last Issue, Dr. Shapiro presented this case report:

A 26-year-old primigravid woman underwent routine ultrasound examination at 22 weeks of gestation. An anechoic cystic structure measuring 15 mm was seen between the left kidney and spleen (Figure 1A, left and right). The kidneys appeared normal and measured 23 mm bilaterally. The amniotic fluid volume was normal. No structural abnormalities were detected and there was a 3-vessel cord. At 28 weeks, the mass had increased in size to 24 mm and was developing some solid components. By 35 weeks, the mass was echogenic and heterogeneous and had increased to 37 mm × 34 mm × 30 mm (Figure 1B).

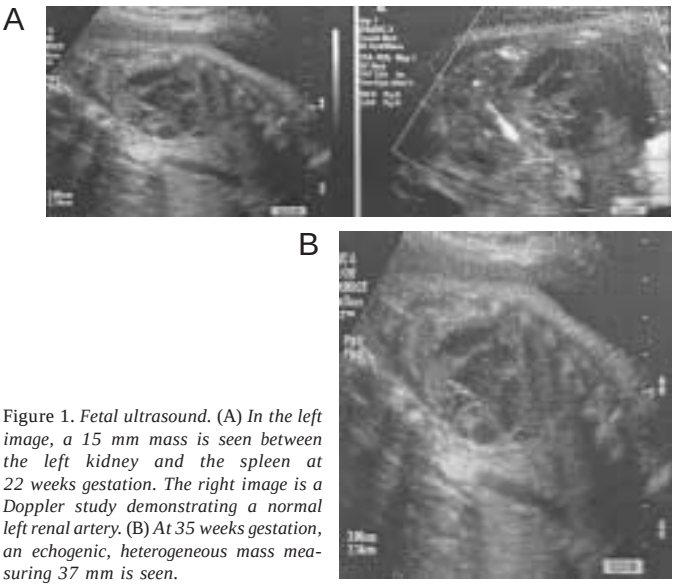

Figure 1. *Fetal ultrasound.* (A) *In the left image, a 15 mm mass is seen between the left kidney and the spleen at 22 weeks gestation. The right image is a Doppler study demonstrating a normal left renal artery.* (B) *At 35 weeks gestation, an echogenic, heterogeneous mass measuring 37 mm is seen.*

The following management options were offered:

The next appropriate step in the management of this patient would be:

1. Observe
2. Early delivery by C-section
3. Amniocentesis for vanillylmandelic acid and homovanillic acid levels
4. Percutaneous biopsy of mass
5. Postnatal left adrenalectomy

Author's Discussion

To understand this case scenario fully, a brief review of the anatomy and embryology of the adrenal gland is necessary. The adrenal glands are paired retroperitoneal structures that lie anteriorly on the superomedial aspect of the upper pole of the kidneys within Gerota's fascia.[1] The adrenal gland is composed of the outer cortex and inner medulla. The adrenal gland weighs 1 g at birth and grows to 4 g to 5 g by late childhood. The average adrenal gland measures 5 cm × 3 cm × 1 cm. The cortex of the gland is yellow, and the gland is flattened with a distinct edge. The adrenal gland has a generous arterial supply from the aorta (1 or more middle adrenal arteries), the inferior phrenic artery (6 to 8 superior adrenal arteries), and the renal artery (1 or more inferior adrenal arteries). Each adrenal gland is drained by only 1 vein, with a short right adrenal vein entering directly into the inferior vena cava (IVC) and a left vein draining into the left renal vein.[1]

The embryology of the adrenal gland is unlike that of most structures.[2] The outer cortex is derived from mesoderm (mesothelium lining the posterior abdominal wall cavity), whereas the inner medulla is derived from an adjacent sympathetic ganglion of neural crest origin. The cortex is first identified during the sixth week of gestation and appears as an aggregate of mesenchymal cells between the dorsal mesentery and the developing gonad. At 7 weeks, the neural crest cells form a mass on the medial side of the fetal cortex. Additional mesenchymal cells surround the mass, giving rise to the permanent cortex. The fetal and permanent cortex then encapsulates the medulla by 8 weeks. Relative to body weight, the fetal adrenal gland is 10 to 20 times larger than the adult adrenal gland, owing to the extensive fetal cortex. The gland loses 35% of its weight during the first 2 to 3 weeks of life, and by 1 year of age the fetal cortex regresses completely. Adrenal cortical zonal differentiation begins late in the fetal period, with only the zona glomerulosa and zona fasciculata present at birth. The zona reticularis is observed at the end of the third year. The adult zonal patterns are seen by 4 years of age.[1,2]

In view of the developmental anatomy of the adrenal gland and its large size, prenatally diagnosed fetal adrenal masses can pose a diagnostic and therapeutic dilemma. What makes these masses even more intriguing is that they can undergo spontaneous resolution before birth.[3] In addition, cysts and hemorrhage can present with atypical sonographic findings, making it difficult to discern whether the mass is benign or malignant.[4,5] The differential diagnosis of a fetal adrenal mass includes adrenal hemorrhage, neuroblastoma (solid and cystic), cystic Wilms tumor, mesoblastic nephroma, lymphangioma, adrenal and renal cysts, duplication of the collecting system, and pulmonary sequestrations.[6-10] Because Beckwith-Wiedemann syndrome is associated with adrenal tumors and adrenal hemorrhage, one must also consider this possibility.[11]

Adrenal hemorrhage occurs in 1.7 per 1000 births, and the incidence of prenatally detected adrenal hemorrhage is 1.9 per 1000 births.[12,13] The exact etiology of adrenal hemorrhage is unknown but is thought to be associated with a sudden increase in venous pressure transmitted from the IVC back to the adrenal gland.[14] The right adrenal vein is short and drains directly into the IVC, which might explain the right-sided predominance of adrenal hemorrhage (70%), whereas the effect of compression or temporary vena caval occlusion would be dampened by the renal vein on the left.[14] In addition, the fetal adrenal gland is more prone to trauma, because it is large and lies anterior to the kidney, and to hemorrhage, owing to its vast arterial supply.[15] Neonatal adrenal hemorrhage might occur spontaneously without an obvious etiology or might be associated with birth trauma, hypoxia, sepsis, hemorrhagic disorders, and hypoprothrombinemia.[7,12]

The sonographic appearance of adrenal hemorrhage depends on the time at which the hemorrhage is detected, that is, the stage of hematoma resolution. Fresh clot after active bleeding will appear as a hyperechogenic irregular mass, and the echogenicity persists after clot retraction. Internal echoes then develop owing to fragmentation of the hemolyzed clot, resulting in multiple interfaces and a more heterogeneous appearance due to the mixed echogenicity.[16] This sonographic picture will become an anechoic or echolucent lesion by 1 month after hematoma formation.[17] Postnatally, calcification in a curvilinear shape in the region of the adrenal suggests prior adrenal hemorrhage.[18] Within the first week of life, infants with adrenal hemorrhage can present with a flank mass (85%), jaundice (80%), and mild anemia (50%).[19] Jaundice is proportional to the degree of hemorrhage and the rapidity of resorption.[14] Boys might present with a scrotal hematoma from blood that has tracked along fat in the inguinal canal or through a patent processus vaginalis.[20]

Neuroblastoma is the most common malignancy in infants, with approximately 37% of cases occurring within the adrenal gland.[3] In the United States, the annual incidence is 10 per 1 million live births.[3,21,22] Although 70% of neuroblastoma cases present with metastases, clinically

evident tumors might mature. Spontaneous regression of in situ neuroblastoma often occurs.[23] In situ neuroblastoma are small nodules of neuroblastoma cells found incidentally, which cannot be distinguished from neuroblastoma. As the fetal adrenal gland develops, clusters of neuroblasts resembling in situ neuroblastoma can be found. Therefore, neuroblastic nodules are thought to be a normal part of the fetal adrenal gland up to approximately 20 weeks. After that time, it is difficult to distinguish in situ neuroblastoma from the neuroblastic nodules. At autopsy, in situ neuroblastoma has been observed in 1 per 224 infant adrenal glands less than 3 months of age. Therefore, the incidence of in situ neuroblastoma is exceedingly greater than the incidence of clinical tumors, and most of these neoplastic lesions undergo spontaneous regression or maturation and remain clinically undetectable.[3,24]

With increased use of prenatal sonography, adrenal masses that are found to be neuroblastoma are detected more frequently.[25] Most cases have been reported after 32 weeks' gestation. The mother is typically asymptomatic in prenatally diagnosed neuroblastoma. Maternal eclampsia or hypertension might be present due to increased circulating catecholamines.[25,26] A retrospective review of 55 cases of prenatally diagnosed neuroblastoma showed an adrenal origin in 93%, and 44% were cystic.[26] Two thirds of the infants had stage 1, 22% had stage 4s, and only 5% had stage 4. Catecholamine levels were increased in only 33%, compared with 85% to 90% of postnatally diagnosed neuroblastomas. This is thought to be because of the relatively small tumors in the infants. Surgery was performed in 85%. Almost all patients had favorable biological features (no N-myc oncogene amplification and no unfavorable deoxyribonucleic acid index). Almost all patients (90%) available for follow-up (50 of 55) were alive at 2 to 120 months.[26] The Italian Neuroblastoma Registry more recently reported 17 prenatally detected neuroblastoma with an adrenal origin (94%).[27] The majority of infants had stage 1 (81%), and primary tumor excision was undertaken at a mean age of 4 weeks. Only 1 patient died from progressive disease. These finding suggest that prenatal screening might be useful.

The observations from the mass screening program instituted in Kyoto, Japan in 1974 for infants 6 months of age are not consistent with the findings of the Italian Neuroblastoma Registry.[28-30] The screening increased the incidence of cases in the first year of life, but there was no decrease in cases presenting in later life. It has been estimated that more than 33% of tumors detected by this infant screening might resolve spontaneously. It is known that infants less than 1 year of age with low-stage disease have a better prognosis.[31] A review of 48 cases detected by screening reported that all patients were alive without evidence of disease.[32] Of the 357 children screened in Kyoto, the overall survival was 97%.[29,30] Because most of these tumors have favorable biologic characteristics, it is not known whether they would have had the same outcome if they presented at an older age with clinical symptoms.[3] It is conceivable that children with unfavorable histology present later and would go undetected by mass infant screening. This might be the case, given that mass screening in Canada increased the incidence of neuroblastoma but did not decrease the incidence of unfavorable high-stage disease in older children.[33,34]

There is a high rate of spontaneous regression, which has been studied in a small subset of children less than 1 year of age (8%–12% of all neuroblastomas) presenting with adrenal and metastatic disease (International Neuroblastoma Staging System stage 4s-localized stage 1 or 2 with dissemination limited to liver, skin, and/or bone marrow but no bone metastases) who receive no treatment.[3] Typically, they have a small adrenal primary tumor, but in 10% no primary tumor is found. The median age for these infants to present is 3 months. Their prognosis is good (80%–87%), and spontaneous regression occurs in many of the tumors, even in the absence of adjuvant therapy.[35-37] The metastases in stage 4s are thought to be nonmalignant clusters of neural crest cells in nonadrenal sites.

The sonographic findings of a neuroblastoma include a heterogeneous echogenic solid tumor, a mixed cystic–solid tumor, or an entirely cystic mass.[3] This explains the dilemma in the prenatal distinction between a large adrenal hemorrhage and neuroblastoma. Because there are no prenatal tests to distinguish these entities, observation is the best recommendation during the prenatal period. Weekly sonographic evaluation will demonstrate resolving hematoma in adrenal hemorrhage, and early Doppler imaging might show a marked rim-shaped pattern of vascularization around the mass, which has been reported angiographically in neonates.[38]

When the mass persists at the time of delivery and the diagnosis remains uncertain, random urine for the 2 major metabolites of catecholamine production, vanillylmandelic acid (VMA) and homovanillic acid (HVA), should be performed.[3] A formal 24-hour collection is preferred but can be difficult to perform in this age group. Although these metabolites are not always detected in the prenatally diagnosed group with neuroblastoma, a negative result and a mass that is becoming progressively smaller suggest that the mass is an adrenal hemorrhage or a spontaneously regressing neuroblastoma. Because of this high spontaneous resolution rate, some investigators recommend a period of 6 months' observation postnatally with close

sonographic follow-up, especially if the mass is smaller than 3 cm and cystic, but this recommendation remains controversial.[26] If the mass is solid, a CT-guided core needle biopsy permits evaluation of the biological features, with surgery reserved for those with unfavorable features, hepatic metastases, and no decrease in tumor size.[26] If the diagnosis remains uncertain, additional tests, including CT and iodine-123 metaiodobenzylguanidine (MIBG) scanning, might be useful.[3]

In our case, the patient was followed to term. The initial sonogram showed a decrease in the size of the complex mass, making the diagnosis of adrenal hemorrhage likely. Random urine tests for HVA and VMA were negative. At 4 months of age, the mass was only 1.5 cm, and areas of calcifications could be seen. At final follow-up at 1 year, only a normal left adrenal gland was noted on ultrasound.

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